Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 9697–9701, October 1995
Neurobiology

Spatial learning with a minislab in the dorsal hippocampus

(spatial memory/water maze/redundancy/distributed memory system/field potentials)

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ABSTRACT **We have determined the volume and location of hippocampal tissue required for normal acquisition of a spatial memory task. Ibotenic acid was used to make bilateral symmetric lesions of 20–100% of hippocampal volume. Even a small transverse block (minislab) of the hippocampus (down to 26% of the total) could support spatial learning in a water maze, provided it was at the septal (dorsal) pole of the hippocampus. Lesions of the septal pole, leaving 60% of the hippocampi intact, caused a learning deficit, although normal electrophysiological responses, synaptic plasticity, and preserved acetylcholinesterase staining argue for adequate function of the remaining tissue. Thus, with an otherwise normal brain, hippocampal-dependent spatial learning only requires a minislab of dorsal hippocampal tissue.**

Converging evidence suggests that functional hippocampal tissue is necessary for allocentric spatial learning and memory. Lesions of the hippocampus disrupt learning and retention of spatial maze tasks (1–5). Recordings from pyramidal (6–9) and granule (9, 10) cells demonstrate firing in relation to the spatial position of the animal (place cells), even after relevant spatial cues are removed from the visual field (8, 11, 12). Although an ensemble of place cells usually covers the entire space of a given environment, the map is nontopographic (1), with adjacent cells having very different place fields (13, 14) and cells representing the same place found at very different mediolateral or dorsoventral locations of the hippocampus (15). Thus, the hippocampus may function as a distributed memory system. If so, it should remain functional when partially damaged.

Previous work with aspiration lesions has shown that lesions have to exceed 10% of the hippocampal tissue to have any impact on spatial learning and that progressively larger dorsal lesions gradually block spatial learning while equally large ventral lesions are ineffective (16). However, the aspiration technique may have caused unintended fiber damage, hampering an estimation of the amount of tissue required for this type of learning. To avoid this problem, we have made fiber-sparing lesions of the hippocampus with ibotenic acid (17). The size of the lesions was varied systematically from 20 to 100% of the total hippocampal tissue, with the spared tissue forming slabs of tissue at the septal or temporal end (Fig. 1). Spatial learning was subsequently tested in an open-field water maze (18), a pool of opaque water with a submerged platform that the rat can locate by navigating according to landmarks around the pool.

MATERIALS AND METHODS

Lesion Procedure. A total of 125 individually housed hooded Lister rats (250–450 g) were anesthetized with tribromoethanol (Avertin, 10 ml/kg) i.p. and received bilateral ibotenic acid-induced lesions of the hippocampus as described (17). Ibotenic acid [Sigma; dissolved in phosphate-buffered saline (pH 7.4) at 10 mg/ml] was injected with a 1-μl Hamilton syringe mounted on the stereotaxic frame and held with a Kopf microinjector. Injections of 0.05–0.10 μl were made over 10–20 s at 28 sites (modified from ref. 17) for a complete hippocampal lesion and at a dorsal or ventral subset of the injection sites for smaller lesions. In sham-operated control rats, the pipette was lowered through the neocortex at an equivalent number of sites; no ibotenic acid was injected. The results reported are based on a subset of 104 animals with acceptable lesions (e.g., no extrahippocampal damage).

Behavioral Testing. Training was conducted in a water maze (18)—a circular pool (2.0 m in diameter) of water (25 ± 1°C; made opaque with latex liquid) located in a well-lit room with numerous visual cues. The rats were given 120 s to localize a submerged platform (10 cm in diameter) 1 cm below the water surface at the center of the northeast (half the animals) or southwest quadrant. Swim tracks were recorded automatically by an image-analyzing device and custom software. The animals were left on the platform for 30 s. For each rat, the platform position was constant throughout acquisition, but start positions were varied randomly. Four consecutive trials were run twice daily (>4 h apart). A transfer test, in which the rats swam for 60 s in the absence of the platform, was conducted at the start of days 5 and 7 (before sessions 9 and 13). Time spent swimming in the four quadrants was recorded. Finally, the rats were trained to escape onto a visible platform (three sessions). Curtains were drawn around the pool, and the platform position was varied from trial to trial.

Evaluation of Lesions. After i.p. injections of Euthatal (sodium pentobarbital at 200 mg/kg), the rats were perfused intracardially with physiological saline and buffered 4% (vol/vol) formaldehyde, and the brains were removed and stored in formaldehyde for >1 week. Frozen sections (30 μm) were cut coronally and stained with thionin. Outlines of the lesions were traced onto 12 coronal line drawings of the hippocampus (19), spaced at 0.5-mm intervals from 1.8 to 7.3 mm posterior to bregma, which allowed determination of the volume of intact hippocampus between each pair of adjacent parallel surfaces. On seven brains with variously sized dorsal or ventral lesions, outlines and estimation of total volume were made by two experimenters (interobserver reliability $r = 0.997$; differences in volume estimates <3%). Rats with intended complete lesions were excluded if <80% of the hippocampus was damaged.

Acetylcholinesterase (AChE). Sections from brains with unilateral dorsal ($n = 2$) or unilateral ventral ($n = 2$) hippocampal lesions, medial septal lesions ($n = 2$), or no lesion ($n = 2$) were stained for AChE 4 days after the lesion, as described (20).

Field Potentials. Rats with ibotenic acid lesions of the ventral or dorsal two-thirds of the hippocampus were anesthetized i.p. with urethane (1.5 g/kg) or tribromoethanol

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Abbreviation: AChE, acetylcholinesterase.

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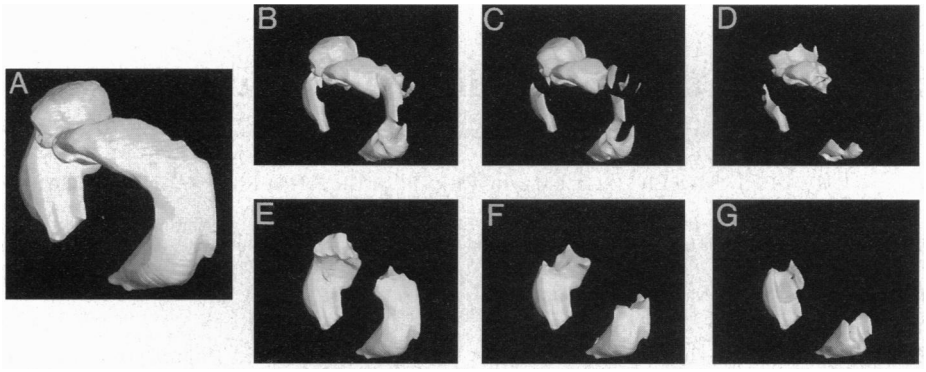

FIG. 1. Three-dimensional reconstruction of a pair of intact hippocampi (*A*) and residual blocks of hippocampal tissue in the dorsal (*B–D*) or ventral (*E–G*) hippocampus of representative animals. The dorsal blocks occupied 62, 50, and 27%, respectively, of the hippocampal volume. The rats with these slabs spent 57.0, 61.0, and 53.0%, respectively, in the platform quadrant on the final transfer test. The small "islands" of ventral tissue in the dorsal 27% animal (*D*) were made up of short sections of intact granule or pyramidal cells; the intrinsic circuitry was incomplete at this level. The ventral blocks occupied volumes of 63, 45, and 26%, with the animals spending 44.9, 24.9, and 21.9% in the training quadrant on the second transfer test, respectively. The blocks were always bilateral.

(Avertin, 10 ml/kg) and placed in a stereotactic instrument. A Teflon-insulated stainless steel recording electrode (75 μm) was positioned in the dentate gyrus (AP 3.8, ML 1.8 or AP 6.2, ML 4.5 mm relative to bregma; $n = 17$), the CA3 (AP 2.5, ML 2.8 or AP 5.8, ML 4.2; $n = 2$), or the CA1 (AP 3.6, ML 2.1; $n = 8$) (where AP is anteroposterior and ML is mediolateral). Bipolar stimulation electrodes (SNEX 100; Rhodes Medical Instruments, Woodland Hills, CA) were placed in the perforant path (AP 8.0, ML 4.1, DV 2.8), the dentate hilus (AP 3.5, ML 1.8, DV 3.0), or the CA3 (AP 2.2, ML 2.2, DV 2.9) (where DV is dorsoventral). Depth profiles and input–output relations (biphasic stimulation, 100–1000 μA, 100-μs half-pulse duration) in response to ipsilateral or contralateral (perforant path, commissural) stimulation were determined at all sites. For mossy fiber potentials, perforant-path signals were first recorded by the dentate stimulation electrode to ensure proper placement in the hilus. Synaptic plasticity was investigated by paired-pulse or tetanic stimulation. The teta-

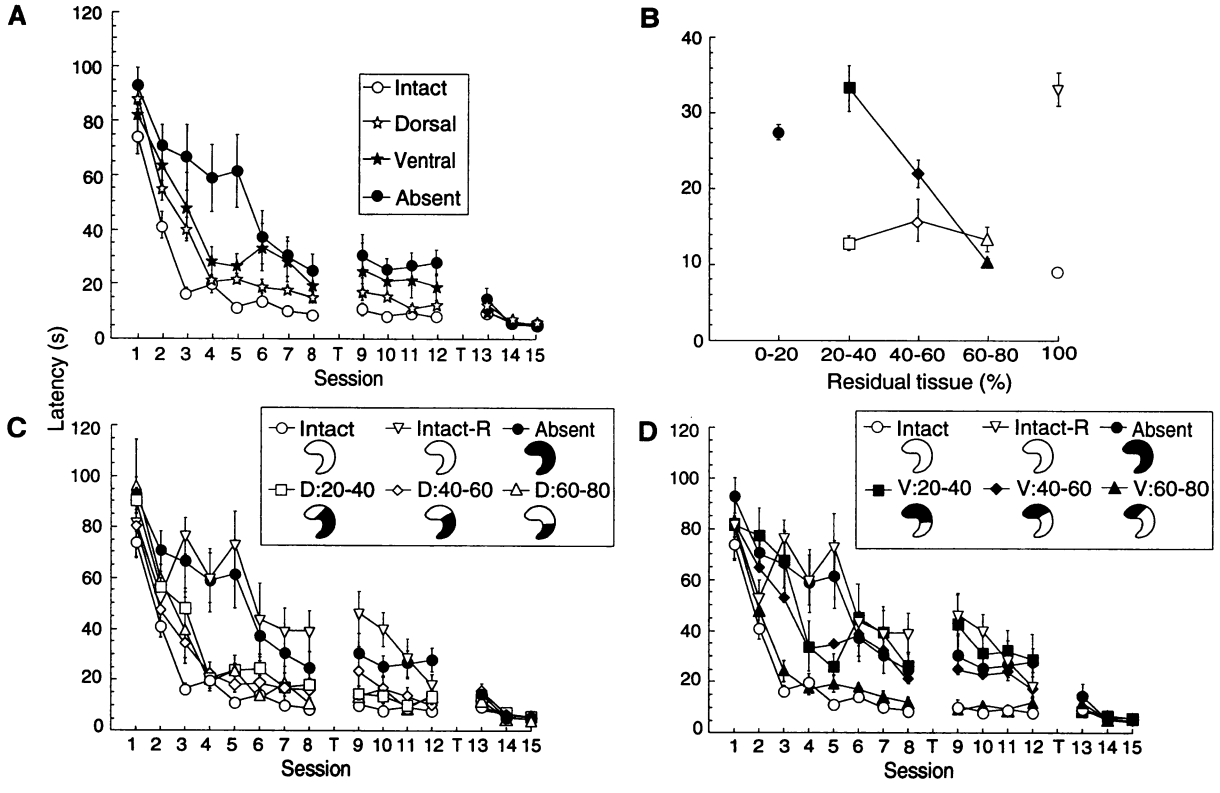

FIG. 2. Mean escape latencies for rats with dorsal and ventral hippocampal lesions in a water-maze task. Two sessions of four consecutive trials were conducted daily. The platform was submerged at a fixed location on sessions 1–12 but was visible on sessions 13–15. Transfer tests (T) were conducted before sessions 9 and 13. (*A*) Latency to escape onto the platform as a function of the dorsoventral location of the remaining intact tissue. Latencies of rats with blocks of between 20 and 80% of hippocampal volume are averaged. (*B*) Relation between size of intact tissue and mean escape latency at the end of the spatial training (between the transfer tests) for rats with blocks of dorsal or ventral tissue. Symbols are as in *C* and *D*. (*C* and *D*) Escape latency as a function of the size of the tissue slabs (percent of total hippocampal volume) in rats with the intact tissue located in the dorsal (D) (*C*) or the ventral (V) (*D*) half of the structure. Intact, intact hippocampi; intact-R, hippocampi intact but platform moved randomly between trials; absent, hippocampi totally lesioned; D:20–40, D:40–60, and D:60–80, dorsal remnant measuring between 20 and 40%, between 40 and 60%, and between 60 and 80% of bilateral hippocampal volume, respectively. V:20–40, V:40–60, and V:60–80, ventral remnant measuring between 20 and 40%, between 40 and 60%, and between 60 and 80% of bilateral hippocampal volume, respectively.

nus was a 1-s train at 100 Hz in the CA1 and eight 400-Hz trains (2 s apart, each consisting of eight pulses) in the dentate gyrus. Paired-pulse stimulation allowed investigation of recurrent inhibition as well. Signals were sampled at 5 or 10 kHz.

RESULTS

Sham-operated rats rapidly learned to find the hidden platform, typically in <10 s on sessions 9–12 (Fig. 2). In contrast, rats with all hippocampal tissue removed stabilized their escape latency at ≈30 s, no different from that of a second sham-operated group for which the platform's position was varied randomly from trial to trial (eight positions, 45° apart; $P > 0.05$), indicating that a complete hippocampal lesion blocks spatial learning (3, 5) in this training protocol as well.

Four findings emerged from our analysis of escape latency in animals with slabs of different size. (*i*) Learning to navigate to the platform proceeded more efficiently when residual tissue was part of the dorsal hippocampus than when it was part of the ventral hippocampus (Fig. 2 *A* and *B*). This finding corroborates the earlier observation with aspiration lesions (16). (*ii*) Rapid place navigation was possible when only a relatively small slab ("minislab") of hippocampal tissue was left intact inside this critical area (Fig. 2 *B* and *C*). In rats in which only 20–40% of tissue (a 2- to 4-mm thick block) was spared at the septal end, the mean escape latency did not differ from those of the sham-operated control rats (sessions 9–12: remaining dorsal tissue 20–40%; 12.8 ± 1.7 s; sham, 9.1 ± 1.0 s; $t(23) = 2.0$; $P > 0.05$). (*iii*) There was a linear relation between the degree of learning deficit and the amount of dorsal hippocampal tissue included in the remaining ventral tissue block (Fig. 2 *B* and *D*). Rats with ventrally located slabs of 20–40% of total hippocampal volume intact performed no better than rats with all tissue removed or rats trained with a platform that was moved randomly from trial to trial (Intact-R). A clear deficit was also seen in animals with the entire ventral hippocampus (40–60% of the total hippocampal tissue) intact. When dorsal tissue was included in the remaining blocks (blocks measuring 60–80%, starting from the ventral pole), normal rates of learning were observed. (*iv*) Within the dorsal hippocampus, the necessary processing could be performed by minislabs oriented in the lamellar plane and located at either the septal pole (dorsal 20–40% group) or, by inference, closer to the border between the dorsal and ventral halves of the hippocampus (ventral 60–80% group). This suggests that spatial acquisition may not be locked to a particular group of cells within the dorsal hippocampus.

A repeated-measures analysis of variance of the escape latencies from sessions 1 to 12 of all spatially trained groups (i.e., except group Intact-R) showed an overall group effect [$F(7,77) = 8.16$; $P < 0.001$], a session effect [$F(11,847) = 140.49$; $P < 0.001$], and a group × session interaction [$F(77,847) = 1.76$; $P < 0.001$]. A comparison of the dorsal and the ventral groups alone on sessions 9–12 (between the transfer tests) gave significant effects of size [$F(2,55) = 3.75$; $P < 0.03$], location [$F(1,55) = 6.31$; $P < 0.02$], and size × location [$F(2,55) = 4.26$; $P < 0.02$]. No group differences were observed on the cued task (sessions 13–15).

These findings were corroborated by examining the precision of the memory for the platform's location. The platform was removed on two trials (transfer tests), one before session 9 and one before session 13. Similar results were observed during both tests. On the final test, the sham-operated rats spent 58.5 ± 3.3% (mean ± SEM) of the swim time in the quadrant previously containing the platform, indicating good

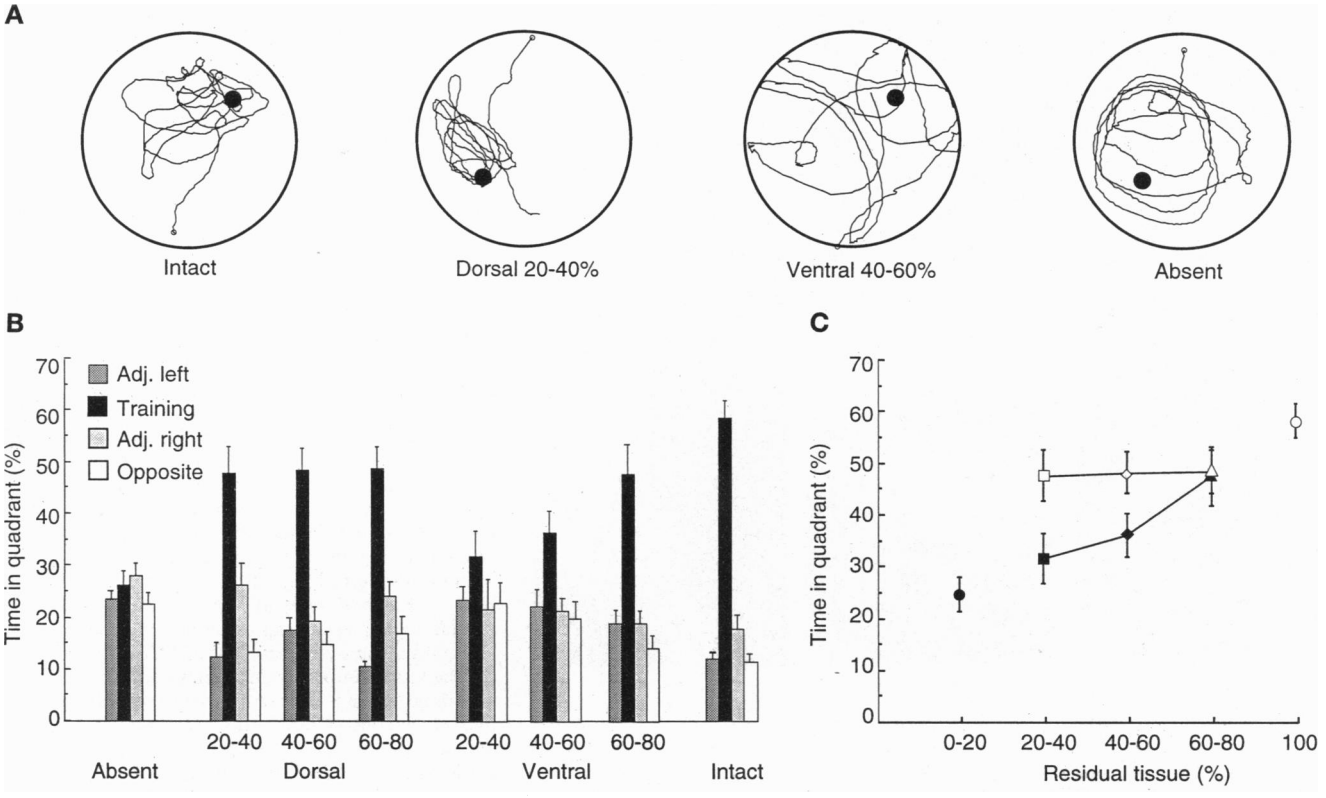

FIG. 3. Performance of rats with variously sized blocks of tissue in the dorsal or ventral hippocampus on the second transfer test. On this test, animals were allowed to swim freely for 60 s in the absence of the platform. (*A*) Records of the search pattern of four representative animals (left to right): a sham-operated (Intact) rat, a rat with a remaining dorsal block of 27% (same as Fig. 1*D*), a rat with a remaining ventral block of 45% (same as Fig. 1*F*), and a rat with a complete hippocampal lesion (14% spared). (*B*) The mean time spent in the four quadrants of the pool by rats with remaining slabs of 20–40%, 40–60%, or 60–80% starting from the dorsal or ventral pole of the hippocampus or with sham lesions (Intact) or complete hippocampal lesions (Absent). (*C*) Relation between size of remaining tissue and time in the training quadrant on the second transfer test. Symbols are as in Fig. 2 *B–D*.

retention of the target position (Fig. 3). Rats with complete hippocampal lesions spent only 26.2 ± 2.5% in the training quadrant (chance = 25%). Animals with a dorsal 20–40% slab remembered the platform location as well as the sham-operated animals [47.9 ± 5.0% of the time was spent in the training quadrant; $t(23) = 1.85$; $P > 0.05$]. Similar performance was seen when 60–80% was spared, starting from the ventral end. However, a reduction of the ventral tissue volume to 40–60% of the total caused a moderate impairment, whereas rats with small ventral slabs remaining (20–40%) were no different from those with a complete lesion. An overall analysis of the time spent in the four quadrants showed a significant group × quadrant effect on both transfer tests [$F(21,231) = 3.40$ and $F(21,231) = 3.68$; P values < 0.001].

The interpretation of the above correlations between hippocampal volume and function rests on the supposition, implied by our use of a fiber-sparing neurotoxin, that the lesions did not substantially alter the normal function of the residual tissue. The border between healthy and damaged tissue was nearly always sharp, suggesting that the density of intact neurons was almost unchanged within most of the minislab (Fig. 4 *A–C*). To investigate whether the residual blocks were deprived of extrinsic connections, we examined the effect of unilateral dorsal or unilateral ventral hippocampal lesions (each 40–60% of the total volume) on AChE staining in the residual tissue 4 days after the lesion. No systematic difference in the amount of AChE stain between the spared part of the hippocampus and the contralateral intact hippocampus could be observed by any of three observers (Fig. 4 *D* and *E*). The AChE stain of the spared part was also similar to that of hippocampal tissue from unoperated rats. In contrast, no AChE stain was detected in the hippocampus of rats given an ibotenic acid lesion in the medial septum, from which axons penetrate all hippocampal subregions and all levels of the septotemporal axis (21–26) (Fig. 4*F*). These observations suggest that extrahippocampal connections passing through areas of ibotenic acid-treated hippocampus, such as cholinergic septohippocampal fibers, were spared by our hippocampal lesion procedure.

It has been hypothesized that residual tissue, although histochemically normal, may have aberrant electrophysiological properties that impair information processing in animals with subtotal hippocampal lesions (27). However, activation of the major excitatory synapses (perforant-path/dentate; mossy-fiber/CA3; Schaffer-collateral/CA1) of the spared blocks gave field potentials with the characteristics previously described for the same synapses in intact preparations (28–32) (Fig. 4*G*). Population spike amplitudes were within the normal range (1–10 mV) in both the dentate gyrus (dorsal and ventral blocks) and the CA1 (measured in dorsal blocks only), indicating that afferent stimulation can activate a large and normal fraction of the cells of the trisynaptic circuit. Both dentate and CA1 potentials showed reversal when the recording electrode was moved through the synaptic layer, testifying to a normal density of the synapses. Large-amplitude potentials could also be elicited by contralateral stimulation (perforant path and

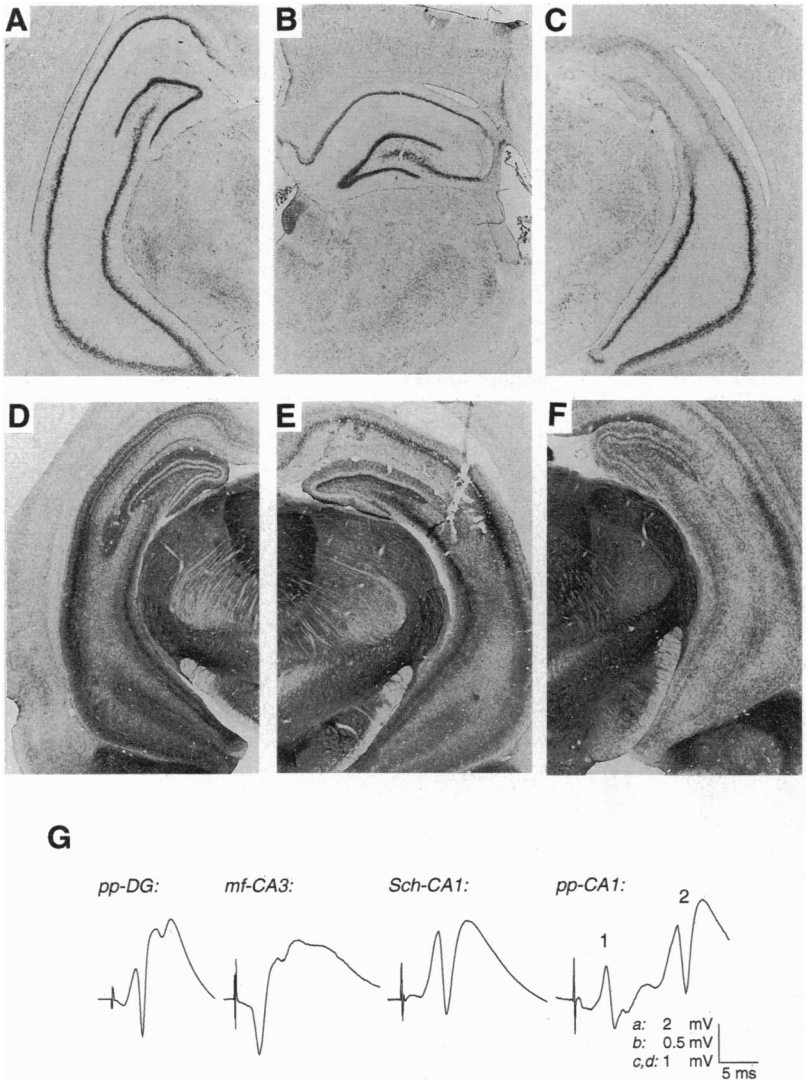

FIG. 4. Histochemical and electrophysiological status of a hippocampal minislab. (*A–C*) Coronal sections showing a thionin stain of neuronal cell bodies in the hippocampus of a sham-operated rat (*A*), a rat with 27% spared at the dorsal end of the hippocampus (also shown in Figs. 1 and 3) (*B*), and a rat with 44% of the hippocampus at the ventral end (*C*). Note the sharp border between healthy and damaged tissue. In *B*, the lesion is limited to the CA3 region. (*D–F*) AChE-stained coronal brain sections in a rat with a unilateral lesion to the dorsal half of the hippocampus (*D*, intact side; *E*, lesioned side) and in a rat with a complete medial septal lesion (*F*). Whereas the medial septal lesion results in a complete loss of AChE stain throughout the hippocampus, staining in the spared ventral slab of hippocampus is not strikingly different from that of the intact contralateral side. (*G*) Field potentials in dorsal slabs of 26–37% of hippocampal volume, recorded from the dentate granule cell layer after stimulation of the perforant path (pp-DG), from the CA3 pyramidal cell layer in response to stimulation of the mossy fibers (mf-CA3), and from the CA1 pyramidal cell layer after stimulation of the Schaffer collaterals (Sch-CA1) or the perforant path (pp-CA1). The perforant-path-evoked CA1 potential shows both an early wave volume conducted from the granule cells (peak 1) and a late CA1 wave with a population spike (peak 2).

commissural pathways). Hippocampal theta activity (7.5–8 Hz) was observed in the remaining tissue in three out of three freely moving rats with extensive ventral lesions. Normal facilitation and inhibition as well as stable long-term potentiation (>45 min) (33) was present in both perforant-path/dentate and Schaffer-collateral/CA1 synapses. The volume of the slabs used for recording ranged from 26 to 37% (mean, 32%) for the dorsal blocks and from 43 to 55% (mean, 49%) for the ventral blocks. Thus, major electrophysiological features of the hippocampal tissue were preserved in blocks of dorsal and ventral hippocampus.

DISCUSSION

The results suggest that spatial learning in rats requires the dorsal but not the ventral hippocampus. These observations are consistent with recent work showing a higher proportion of place cells, as well as more focused place fields, in the dorsal than in the ventral hippocampus (15). This functional dissociation along the septotemporal axis is probably related to the different connectivity of the dorsal and the ventral hippocampus (34–40). Relevant sensory information from the association cortices is conveyed to entorhinal and perirhinal regions projecting to the dorsal two-thirds of the hippocampus. The ventral hippocampus, in contrast, is essentially connected with subcortical areas.

They also indicate that spatial learning requires the integrity of only a 2- to 4-mm wide transversely oriented minislab. Although the average direction of the intrahippocampal excitatory pathways is in the lamellar plane (41), which is probably intact in the minislab preparation (48), signals normally spread for more than a millimeter on either side of the main vector (42–46). The present results suggest that long-distance septotemporal divergence is not essential for the spatial learning task employed.

Importantly, learning does not seem to require a specific portion of the dorsal hippocampus. Within the critical area of the dorsal hippocampus, the minislab can be placed at different positions and still subserve spatial learning. Thus, this tissue may contain multiple facultative networks for spatial learning. Unlike primary cortical areas, the intact hippocampus may contain, or have access to, multiple representations of a given spatial environment, a finding consistent with the nontopographical mapping of hippocampal place cells (13, 14).

Finally, the findings shed light on the redundancy in the hippocampal memory system. Efficient spatial learning required only 20–40% of the total hippocampus, corresponding to about half of the portion of the hippocampus that receives relevant sensory input [the dorsal two-thirds (34–40)]. These numbers probably underestimate the redundancy, as the trisynaptic circuit along the edges of a minislab may be broken due to lesions of neighboring areas. Our results are compatible with models of the hippocampus as a distributed associative memory system that predict preservation of function after partial lesions (47).

We thank P. Papageorgiou and A. Bissel (VOXAR, Edinburgh) for help with the three-dimensional reconstruction; Drs. T. Lømo and M. Simmen for comments on the manuscript; and P. Spooner, E. Hansen, and L. Scholte for technical assistance. This work was supported by grants from the Institute of Psychology, University of Oslo (M.-B.M. and E.I.M.), the Norwegian Research Council (M.-B.M., E.I.M., and P.A.), the Human Frontiers Science Program (M.-B.M., E.I.M., P.A., R.G.M.M.), the U.K. Medical Research Council (R.G.M.M.), and The Stanley Davidson Trust (R.G.M.M.).

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